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(54) **A generic zero order controlled drug delivery system.**

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D scription

Ar adily manufactured device which will dependably release an activ material (.g., a pharmaceutical agent, a cleanser or a deodorizer) at a zero-order rate into a fluid medium (gaseous or liquid) has remained an elusive goal, particularly when the device is in th form of a tablet for controlled in vivo release of a pharmaceutical agent into a biological fluid (e.g., the fluid of the gastrointestinal tract).

An early proposed method was that of Jacobs, U.S. Patant 3,113,076 (1963) In which the drug was combined in a suitable carrier and tablats obtained by an extrusion method. The principla was to form tablets with approximately equal outer and "inner" surfaces, the latter accessed by aparture(s). As the axterior surfaca is dissolved, the area decreases, while as the inner surfaca dissolves, the surface area increases. Absent diffusion effects respecting the interior surface, the total surface, and thus rate of solution, would remain relativaly constant. In its simplest form, Jacobs' tablet is a cylinder achieving equal inner surfaca by a multiplicity of cylindrical holes which are parallel to the axis of the outer cylinder, and accessed by the multiple apertures at each end of the cylinder. A related, but more sophisticated device, which now takas into account diffusion effacts with respect to the inner surface, is that of Brooke, U.S. Patent 3,851,648 (1974). Brooke discloses a cylindrical container, closed at the ends, with a cavity in the shape of a cylinder sector with the aperture in the form of a slot in the outar surface of cylindar (parallel to the axis of the cylinder), said slot at the apex of the cylindar sector cavity. See also Brooke et al., J. Pharm. Sci. 66, pp. 159-162 (1977). In practice, this device produces releasa rates which are initially high ; Lipper et al., J. Pharm. Sci. 66, pp. 163-164 (1977). It is suggested that the device might be implanted into body cavities, but thara is no suggestion for use of this device in the form of an ordinary tablet, or for a method of manufacturing such a tablat. Further, tha device described by Brooke contains an inner compartment fully or partially filled with active substance laading to the surface of tha device through a cavity.

EP-A-153070 describes a laminate device having a core sheet formed of a polymer matrix containing medicament to ba released at a controlled rate, the core sheet being sandwiched between impervious films. The core sheet and films are perforated with macroholes. GB-A-1372040 discloses a spherical tablet having a perforatad coating through which the active ingredient is released at an exponentially increasing rate.

We have now discovered a device for tha controlled relaasa of one or more active substances into a fluid madium at a substantially constant rate (i.e., zero-order) which comprises said substance homoganeously dispersad, with or without inart excipients, and contalned substantially in the shape of a tablet or bolus by maans of an all-covering, essentially impermeable wall or coating excapt for ne or more strips of removed wall or coatlng from the sida of said device.

A pr ferred feature of said device is a flat cylindrical side, that is the generator of the side surface is straight, and conv x top and bottom. Within this preferred embodiment is especially preferrad a cylindrical tablet or bolus having more than ona strips of wall or coating removed from the side of said tablet or bolus, wherain the width of said strips can be the same of differant from each other.

A second preferred featura of said davice is that wherein the substance is biologically active. Especially preferred is a substance having germicidal or pharmacological activity or activity in preventing or reducing odors in or emanating from a fluid medium.

Also part of the present invention is a bolus for oral administration into tha raticulum or rumen of a ruminant mammal, said bolus being retalned in said rumen or reticulum and releasing one or mora active substances into the environment of said rumen or raticulum at a substantially constant rate (i.e., zero-order) over a prolonged period of time, which comprises said activa substance or substances homoganeously dispersed in a matrix and contalned by means of an all-covering, assentially impermeable wall or coating except for one or more strips of removed wall or coating from the side of said bolus.

Praferred is a bolus containing morantel or a pharmaceutically acceptable salt thereof as the active substance.

An additional aspact of the present invantion is a tablat for oral administration to a mammal which releasas a pharmaceutically activa substance into the fluid of the gastrointestinal track of said mammal at a substantially constant rate (i.e., zero-order) over an appraciabla time interval which comprises said substance homogeneously dispersed, with or without one or more pharmaceutically accaptable excipients and contalned by means of an all-covering, assentially impermeable wall or coating except for one or more strips of removed wall or coating from the sida of said tablet.

Preferred is a tablat wharain the substance is an antihypertensive agent. Especially prefarred within this group are prazosin, nifedipine, trimazosin and doxazosin.

Also prefarred is a tablet wherein the substance is an antianxiety agent. Especially preferred within this group is hydroxyzine and sertraline.

Also preferred is a tablet wharein the substance is a bronchodilator. Especially preferred is the bronchodilator pirbutarol.

Also within tha prefarred embodimant is a tablet wharein the substance is a hypoglycemic agent. Especially preferred is glipizide.

Also preferred is a tablet wh r In the substance is a cough or cold agent. Especially pref rred are bromphenlramine dexbromph nlramine and chlorph nlramine maleates, phenylephrine and pseudoephedrine hydrochlorides and cetirizine.

As applied in the present invention, the term "fluid" is Intend d to ncompass either liquid or gaseous, the term "essentially impermeable wall or coating" embraces any material which prevents any substantial movement of the contents or of the surrounding fluid across the wall or coating, and the term "pharmaceutically active substance" is Intended to encompass, but Is not restricted to analgesics, anorexics, anthelmintics, antibacterials, anticonvulsants, antifungals, antidepressants, antibiotics, antihistamines, antiulcer drugs, antihypertensives, bronchodilators, immunosuppressants, aldose reductase Inhibitors, antiinflammatories and blood glucose lowering agents. The "active substances" used individually or in combination in the bolus device of the present invention Include anthelmintics, including morantel, pyrantel, oxantel, piperzine, diethylcarbamazine, levamisole, tetramisole, and hygromycin B ; antibacterials including sulfa drugs such as sulfadiazine, sulfanilamide, sulfathiazole, sulfamethazine, sulfaguanidine, and sulfapyridine ; tetracyclines, such as 5-oxytetracycline, chlorotetracycline, doxycycline and Mannich bases thereof ; penicillins such as ampicillin, penicillin G ; aminoglycosides such as neomycin, streptomycin, apramycin, bacitracin as its zinc or methyl disalicyclic acid derivative ; macrolides such as erythromycin, oleandomycin and tylosin ; antibacterial growth promotants such as avoparicin, polymyxin, lincomycin, bambermycin and efrotomycin ; hormonal growth promotants including diethylstilbestrol, zearalanol and melengestrol acetate ; antiparasitic agents such as amprolium; nutritional agents such as salts of magnesium, selenium copper and vitamins such as thiamine hydrochloride ; molluscicides such as N-trityImorphine ; and bloat prevention agents such as alcohol ethoxylates and poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene)-polymers, e.g. poloxalene.

Devices according to embodiments of the invention will now be described with reference to the accompanying drawings in which :

Figure 1 shows an oblique view of a tablet of the present invention, prepared on a conventional tabletting machine, then coated and uncoated in strips on the side of the tablet.

Figure 2 shows an oblique view of a bolus of the present invention, prepared in a conventional manner, then coated and the coating removed in strips along the side of the bolus.

Figures 3 and 4 show alternative cross sections of the bolus of Figure 2. The cross section of Figure 3 shows the bolus with a cylindrical metal core and the location of the strips of coating removed along the side. Figure 4 shows a similar bolus with a hexagon shaped metal core and the location of the strips of coating removed from the side of the bolus.

Figure 5 shows a side view of a device with a different shape which Is coated and the coating r moved in strips which are equidistant.

Figure 6 shows an oblique view of a bolus prepared as that in Figure 2 in which the coating is removed in strips from the side of said bolus around the circumference of the device at right angles to the longitudinal axis of the device. A heavy insert can be used in the center of the device, if necessary.

Figure 7 shows an oblique view of a bolus prepared as that in Figure 5 in which the coating is removed in strips from the side, at an angle to the longitudinal axis of the bolus.

Figures 8-10 show the rate of release of active substances from tablets and boluses prepared in the specific examples below.

Figures 11 and 12 show side and end views, respectively, of a cutting machine used to remove the coating in strips on the aforementioned devices.

The present invention is readily practiced, offering advantages over other controlled release devices. One important advantage is the nearly constant (zero-order) rate of release of active ingredient over virtually the entire release period.

The outstanding feature of the devices of the present invention is the simplicity with which they can be prepared. When the device is a bolus or an ordinary cylindrical or drum shaped tablet the active ingredient or ingredients are blended with an inert excipients and formed into the appropriate shape using conventional tablet presses or bolus molds.

The use of inert ingredients or excipients aid in tablet or bolus formation and also in controlling the rate of release of the active substance or substances from the appropriate device. An inert ingredient can be of the dissolution type, wherein it is eroding or dissolving at the same time as the active substance, or it can form a matrix which is not soluble, and retains the shape of the device as the active ingredient is released. The excipients include ethylene-vinyl acetate and ethyl cellulose. A portion of the inactive ingredients of the bolus device, in addition to being that described above, can be a metal core, usually steel. This core is employed to insure that the bolus remains in the rumen or reticulum of the animal being treated, and is not prematurally regurgitated. In cases where a metal insert is deemed undesirable, it can be replaced with a ceramic core or some other dense material.

Following the formation of the tablet or bolus, a coating is applied using coating pans or some other available coating t chnology. A variety of imperme-

abl coating materials can b employed, such as ethylene-vinyl acetate.

Once the tablet is coated, a strip or strips are removed from the side. When more than one strip is removed, the removed strips should be placed equidistant from each other around the side of the tablet. Such a tablet is illustrated in Figure 1, in oblique, having substantially imp rm able all-covering wall or coating 10 except for removed wall or coating as strips equidistant from each other 11, 12 and 13.

Similarly, a shaped bolus is coated by conventional means as illustrated in Figure 2, in oblique, the coating 22 then removed in strips 20 and 21 from the side of the bolus. As previously indicated, the strips are spaced equidistant from each other. In order to prevent regurgitation of the bolus device by the animal being treated it is advantageous to use a weighted core in the bolus. This may consist of steel shot or rod running the length of the device. The cross section shape of the rod can be circular as illustrated in Figure 3, 32 such that the rod is centered in the middle of the device, with the active substance forming a cylindrical shell around the rod. The removed strips of wall or coating 33 are spaced equidistant from each other on the side of the bolus. The shape of the metal insert can vary. Figure 4 illustrates the cross section of a bolus device in which the hollow cylindrical shell is filled with a rod having a hexagonal cross section 42 shape. In this case the removed strips of wall or coating are placed equidistant from each other and opposite the midpoint of each hexagon side. In a similar manner, a bolus device with four strips removed would accomodate a rod with a square shaped rod, the strips placed equidistant from each other and opposite the midpoint of each side of the square rod side.

The application of the present invention is also meant to apply to cylindrical devices in which the cross section of the bottom of said device is larger than the cross section at the top. An example of such a controlled release device is illustrated in Figure 5, in side view, 53. Following the conventional formation and coating of such a device the coating 52 is removed as a strip 51 on the side of the device. In this instance, because of the tapering nature of the device, the strip removed is wider at the portion of the device which is wider and tapers to a narrower width at that end of the device which is more narrow. The adjustment of the strip width to the corresponding tapering of the device allows for a prolongation of the zero-order release of the active substance.

In addition, to the strip or strips of coating being removed parallel to the longitudinal axis of the device, they can also be removed in other manners and still allow the device to deliver the active substance at a zero-order release rate. Figure 6 illustrates in oblique view of the bolus similar to that in Figure 2 with the coating 62 removed in a strip or series of strips 61 circling around the surface at a right angle to the longitudinal axis of th device. If more than one strip is r moved the strip should be removed equidistant from on anoth r. Similarly, Figure 7 illustrates the same bolus in which the coating 72 is remov d in strips 71 at an angle to th longitudinal axis of the bolus. Again, if more than one strip is removed they should be placed equidistant from one another.

As previously mentioned, the devices of the present invention can be formed into the various shapes described with excipients, the active compound will generally be thoroughly blended with conventional, pharmaceutically acceptable excipients to form either devices of the dissolution type (where the excipient disintegrates and generally dissolves along with the active ingredient) or of the matrix type (where the active ingredient diffuses into the surrounding medium leaving the matrix intact). Excipients typically used for either purpose include lactose, sucrose, calcium lactate, magnesium stearate, ethyl cellulose and ethylene vinyl acetate copolymer.

Once formed the tablets or boluses are optionally compression coated (see Ellis et al., Chapter 10, "Tablet Coating", in "The Theory and Practice of Industrial Pharmacy", Lachman et al., eds., Lea and Febiger, 1970, p. 207 et. seq.) to form cylindrical or drum shaped tablets and boluses as illustrated in Figures 1-7. The coating materials which are used are substantially impermeable to the device contents and to the ultimate gastrointestinal fluid. A wide range of coating materials can be used and the water flux through the coating can be minimized by the selection of a proper coating thickness. Coating materials which are biodegradable over a longer period can also be employed. On an experimental scale, coating is conveniently accomplished by repeated dipping of the device in a volatile organic solution of a polymer such as ethylene-vinyl acetate copolymer.

The final step in the preparation of the devices of the present invention comprises the removal of the essentially impermeable wall or coating in strips as previously described. Removal of the coating can be by simple manual cutting, but on a commercial scale is carried out by machine cutting, laser cutting or high pressure water cutting.

A cutting machine useful for removing strips of coating from the devices of the present invention is shown in Figures 11 and 12. In the first figure, a side view of the cutting machine, a vibrating feeder 94 aligns the coated devices 92 as they pass through a portal leading to three drive belts 91 and 97 (two shown) driven by drive belt motors 99 (shown) and supported by a drive belt support 98 (shown). As the devices are moved along by the drive belt they encounter three cutters 93 and 95 (shown) driven by cutter motors 96 (shown) the blades of said cutter rotating counter to the direction of the movement of the devices.

The second figure, Figure 12, shows an end view

of th cutting machine showing the vibrating feeder 81, the three drive belts 82, 85 and 88 driven by drive belt motors 87 (shows) and the three cutters 83, 86 and 90 driven by cutter motors 89 (shown). The position of the device 84 as it is positioned in relation to th cutters and drive belts is shown.

This particular cutting machine is set to r mov the coating on the sides of the devices at three points equidistant from each other. Similar types of cutting machines can be employed to make more or less cuts to the sides of the devices, as previously mentioned.

The strip or strips of coating which are removed can vary in width. Wider width strips expose more of the active substance to the fluid medium and release the active material more quickly. While the width of the strips can be varied, the release rate from the herein described devices is still zero-order. The ratio of the width of the strip of removed coeting or wall to the circumference of the device can be from 1 : 16 to 1 : 100.

As previously mentioned, if more than one strip of coating is removed they may or may not be of the same width. Further, in the device in Figure 5, the strip removed can vary in width from top to bottom of side of the device. The uncoated strip dimension can be kept in proportion to the diameter of the device at any point.

The finished devices are tested in vitro for zero order release of the active ingredient as detailed in the Examples below. The in vitro tests are correlated with the in vivo rate of release, for example, by measuring the blood levels of an active agent over time following ingestion of the device.

When the present bolus device is used for delivery of active agent(s) to a ruminant mammal it will generally be in the form of a bolus for long term delivery (e.g., 2 weeks or more) in the rumeno-reticular sac (rumen or reticulum) of a ruminant animal, dosed orally by means of a conventional bolling gun. The bolus is designed so that it is of a size that will permit introduction into the rumeno-reticular sac via the esophagus, and retained there by means of its weight, or by means of change in shape which occurs after its administration.

The following examples are given by way of illustration.

EXAMPLE 1

Zero-Order Release Tablets-Morantel Tartrate "A"-Device

A tablet consisting of morantel tartrate and ethylene vinyl acetate copolymer (50 : 50 ; w : w) weighing 119 mg was coated with ethylene vinyl acetate by dip-coating the tablet in a 10% solution of ethylene vinyl acetate copolymer in toluene at 55°C three times, allowing the tablet to dry each time before the next coating. Th coating n th side of the tablet, which measured 2.5 mm (0.098") in thickness and 8.5 mm (0.334") in diameter, was removed as a strip 1.0 mm (0.040") wide and 2.5 cm (0.098") long at two positions diametrically opposit each other using a scalpel.

The in vitro release of morantel tartrate from the tablet was det rmin d as a function of time. Th test was conducted in water at 40°C. The quantity of morantel tartrate released at a given point in time was determined by direct ultraviolet spectrophotometric assay of a withdrawn sample.

The results of the test are shown in Figure 8 as "A" Device.

"B" Device

The above procedure was repeated except that strips of coating were removed at four positions on the side of the tablet. Two measured 1.0 mm (0.040") wide by 2.5 mm (0.098") long and were made diametrically opposite each other. The second two measured 0.15 mm (0.006") wide and 2.5 mm (0.098") long and were made diametrically opposite each other and oriented at 90° to the first two removed strips.

The results on the release of morantel tartrate in shown in Figure as "B" Device.

EXAMPLE 2

Zero-Order Release Disk-Morantel Tartrate

Two disks consisting of morantel tartrate and ethylene vinyl acetate copolymer (50 : 50 ; w : w) and measuring 25.4 mm (1") in diameter and 1.9 mm (0.075") thick were coated as described in Example 1. In the first disk the coating was removed on the side at 5 places equidistant from each other. The width of the strip removed was 2 mm by the thickness of the disk. The coating of the second disk was removed in a similar manner from six positions equidistant from each other on the side of the disk.

The release of morantel tartrate was measured as described in Example 1 and the results are shown in Figure 9, the disk having the coating removed from 5 positions being # 1 and the disk wherein the coating was removed from six positions being # 2.

EXAMPLE 3

Zero-Order Release Bolus-Morantel Tartrate

Five boluses were prepared, using a compression mold with a centered insert in the shape of a hexagon rod 10 cm (4") in length and a face width of 14.3 mm (9/16") containing a 50-50 mixture by weight of morantel tartrate and ethylene vinyl acetate copolymer. The bolus s w re dip coated using a 10%

toluene solution of thyl n vinyl acetate copolymer. The boluses were dipped three tim s, each time allowing the coating to dry.

Each bolus contained 36.5 g of the 50-50 mixture.

Six strips of coating were removed from each bolus m asuring about 2 mm (0.080") wide and the length of th bolus. The strips were removed opposite the face of the hexagonal insert and spaced equidistant from each other. The ends of the bolus were sealed to prevent loss of the active substance using two coats of ethylene vinyl acetate copolymer.

The boluses were then tested as described In Example 1 for the release of morantel tartrate and the results summarized in Figure 10.

EXAMPLE 4

Zero-Order Release Bolus-Terramycin Hydrochloride

A bolus consisting of a mixture of terramycin hydrochloride and ethylene vinyl acetate copolymer (50-50 by weight) was prepared as in Example 3, with exception that a cylindrical plastic insert was employed in place of the stainless steel.

The formed bolus was coated with ethylene vinyl acetate copolymer using a 10% ethylene vinyl acetate copolymer-toluene solution. The device was dip-coated three times, being allowed to dry each time before the next coating.

The coating was removed at six positions on the side equidistannt from each other. Each strip was 2 mm (0.080") wide and 10 cm (4") long, the length of the bolus.

The ends of the bolus were sealed with ethylene vinyl acetate copolymer by dip-coating.

The bolus contained 42.57 g of the mixture of terramycin hydrochloride and copolymer.

EXAMPLE 5

Diaper Pail Deodorant

Following the procedure of Example 1, a large tablet measuring 6.3 cm (2.5") in diameter and 2,5 cm (1") thick, and comprised of a mixture consisting of p-dichlorobenzene and polyethylene glycol (average molecular weight 1000) in 60 : 40 portions, is dip-coated with ethylene vinyl acetate copolymer. Strips of the coating measuring 1.6 mm (1/16") wide by 2.5 (1") long are removed at four positions on the side of the tablet equidistant from another. The device is used as a deodorant in the air space of a diaper pail, where it is effective for at least several days to several weeks.

EXAMPLE 6

Zero-Order Release Tablet-Sodium Benzoat

A 350 mg tabet consiting of 30% sodium benzoate 45% thyl cellulose, 24.5% spray dried lactose and 0.5% magn sium st arate by weight Is dip coated with thylene vinyl acetate copolym r three times, allowing the tablet to dry each time. Three strips of coating measuring 1 mm wide are removed from the side of the tablet equidistant from one another. When tested according to the procedure described In Example 1, the sodium benzoate is released at a constant rate (zero-order release).

EXAMPLE 7

Toilet Tank Germicide

In a manner similar to Example 1, a tablet measuring 7.6 cm (3") in diameter and 2.5 cm (1") thick and comprised of O-phenylphenol and p-dioxanone in a weight ratio of 1 : 10 is dip-coated with ethylene vinyl acetate copolymer and five strips of coating measuring 1.6 mm (1/16") wide by 2.5 (1") long are removed from the side of the tablet equidistant from each other.

The tablet is used in a toilet tank, where it provides effective germicidal action for several weeks under normal use conditions.

Claims

Claims for the Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE, ES

1. A device for the controlled release of one or more active substances into a fluid medium at a constant rate which comprises said substance homogeneously dispersed, with or without one or more inert excipients, and contained In the shape of a generally cylindrical tablet or bolus by means of an all-covering impermeable wall or coating except for one or more strips of removed wall or coating from the side of said device.

2. A device of claim 1, wherein the side defines a cylinder and the top and bottom are convex.

3. A device of claim 2, wherein more than one strip of wall or coating is removed from the side of said device, the strips removed having the same or different widths.

4. A device according to any preceding claim, wherein the substance is biologically active.

5. A device of claim 4, wherein the activity of the substance is to prevent or reduce odours In or emanating from the fluid medium, or the substance has germicidal or pharmacological activity.

6. A device according to claim 1 comprising a bolus for oral administration into the reticulum or rumen of a ruminant mammal, said bolus being retained in said rumen or reticulum and releasing one or more active substances into the environment of said rumen or reticulum at a constant rate over a prolonged period of time.

7. A bolus of claim 6, wherein the active substance is morantel or a pharmaceutically acceptable salt thereof in a polymer matrix.

8. A device according to claim 1, comprising a tablet for oral administration to a mammal which releases a pharmaceutically active substance into the fluid of the gastrointestinal tract of said mammal at a constant rate over an appreciable time interval.

9. A tablet of claim 8, wherein the substance is an antihypertensive.

10. A tablet of claim 9, wherein the substance is prazosin, nifedipine, trimazosin, or doxazosin.

11. A tablet of claim 8, wherein the substance is an antianxiety agent.

12. A tablet of claim 11, wherein the substance is hydroxyzine or sertraline.

13. A tablet of claim 8, wherein the substance is a bronchodilator.

14. A tablet of claim 13, wherein the substance is pirbuterol.

15. A tablet of claim 8, wherein the substance is a blood-glucose lowering agent.

16. A tablet of claim 15, wherein the substance is glipizide.

17. A tablet of claim 8, wherein the substance is a cough or cold agent.

18. A tablet of claim 17, wherein the substance is brompheniramine maleate, chlorpheniramine maleate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, cetirizine or dexbrompheniramine maleate.

Claims for the Contracting State : GR

1. A method of making a device for the controlled release of one or more active substances into a fluid medium at a constant rate which comprises dispersing said substances homogeneously, with or without one or more inert excipients, and containing the same substantially in the shape of a generally cylindrical tablet or bolus by means of an all-covering impermeable wall or coating, and removing one or more strips of the wall or coating from the side of the tablet or bolus.

2. A method according to claim 1, wherein the side defines a cylinder and the top and bottom are convex.

3. A method according to claim 2, wherein more than one strip of wall or coating is removed from the side of said device, the strips removed having the same of different widths.

4. A method according to any preceding claim, wherein the substance is biologically activ .

5. A method according to claim 4, wherein the activity of the substance is to prevent or reduce odours in or emanating from the fluid medium, or the subtance has germicidal or pharmacological activity.

6. A method according to claim 1 of making a bolus for oral administration into the reticulum or rumen of a ruminant mammal, said bolus being retained in said rumen or reticulum and releasing one or more active substances into the environment of said rumen or reticulum at a constant rate over a prolonged period of time.

7. A method according to claim 6, wherein the active substance is morantel or a pharmaceutically acceptable salt thereof in a polymer matrix.

8. A method according to claim 1 of making a tablet for oral administration to a mammal which releases a pharmaceutically active substance into the fluid of the gastrointestinal tract of said mammal at a constant rate over an appreciable time interval.

9. A method according to claim 8, wherein the substance is an antihypertensive.

10. A method according to claim 9, wherein the substance prazosin, nifedipine, trimazosin, or doxazosin.

11. A method according to claim 8, wherein the substance is an antianxiety agent.

12. A method according to claim 11, wherein the substance is hydroxyzine or sertraline.

13. A method according to claim 8, wherein the substance is a bronchodilator.

14. A method according to claim 13, wherein the substance is pirbuterol.

15. A method according to claim 8, wherein the substance a blood-glucose lowering agent.

16. A method according to claim 15, wherein the substance is glipizide.

17. A method according to claim 8, wherein the substance is a cough or cold agent.

18. A method according to claim 17, wherein the substance is brompheniramine maleate, chlorpheniramine maleate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, cetirizine or dexbrompheniramine maleate.

Ansprüche

Patentansprüche für die Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE, ES

1. Vorrichtung für die gesteuerte Freigabe einer oder mehrerer aktiver Substanzen in ein flüssiges Medium in konstanter Menge, die diese Substanz homogen dispergiert umfaßt, mit oder ohne einem oder mehreren inerten Arzneistoffträgern, und die in

dar Form iner gängigen zylindrischen Tablette oder eines Bolus enthalten ist mit Hilfe einer all-umschließenden undurchlässigen Wand oder eines Überzuges außer ines oder mehrerer Streifen von d n S iten dieser Vorrichtung entfernter Wand od r Überzuges.

2. Vorrichtung nach Anspruch 1, worin die Seite ainen Zylinder definiert und die Ober- und Unters iten konvex sind.

3. Vorrichtung nach Anspruch 2, worin mehr als ein Streifen der Wand oder das Überzuges von der Saite der Vorrichtung entfernt sind, wobei die entfarnten Streifen die gleiche oder unterschiedliche Breiten haben.

4. Vorrichtung nach einem der vorstehenden Ansprüche, worin die Substanz biologisch aktiv ist.

5. Vorrichtung nach Anspruch 4, worin die Wirksamkeit der Substanz darin besteht Gerüche in dem oder austretend aus dem flüssigen Medium zu verhindern oder zu reduzieren, oder die Substanz eine keimtötende oder pharmakologische Wirksamkeit hat.

6. Vorrichtung nach Anspruch 1 umfassend einen Bolus für die orale Verabreichung in den Netzmagen oder den Pansen eines wiederkäuenden Säugetieres, wobei der Bolus im Pansen oder Netzmagen zurückgahalten wird und eine oder mehrere aktive Substanzen in die Umgebung im Pansen oder Netzmagan entläßt in einer konstanten Menge über einen längeren Zeitraum.

7. Bolus nach Anspruch 6, worin die aktive Substanz Morantel oder ein pharmazeutisch annehmbares Salz davon in einer Polymermatrix ist.

8. Vorrichtung nach Anspruch 1, umfassend eine Tablette zur oralen Verabreichung für ein Säugetier, die eine pharmzeutisch wirksame Substanz in die Flüssigkeit des gastrointestinalen Traktes dieses Säugetieres entläßt in einer konstanten Menge über ein nennenswertes Zeitintervall.

9. Tablette nach Anspruch 8, worin die Substanz gegen Hypertonie ist.

10. Tablatte nach Anspruch 9, worin die Substanz Prazosin, Nifadipin, Trimazosin oder Doxazosin ist.

11. Tablatte nach Anspruch 8, worin die Substanz ain Beruhigungsmittal ist.

12. Tablette nach Anspruch 11, worin die Substanz Hydroxyzin oder Sertralin ist.

13. Tablette nach Anspruch 8, worin die Substanz ein Bronchodilator ist.

14. Tabletta nach Anspruch 13, worin die Substanz Pirbuterol ist.

15. Tablette nach Anspruch 8, worin die Substanz ain blutzuckersankendas Mittel ist.

16. Tablette nach Anspruch 15, worin dia Substanz Glipizid ist.

17. Tablette nach Anspruch 8, worin die Substanz ein Husten- oder Erkältungsmittel ist.

18. Tablette nach Anspruch 17, worin die Substanz Brompheniraminmal at, Chlorpheniramin-maleat, Ph nylephrine-hydrochl rid, Pseudoephadrin-hydrochlorid, Cetirizin- oder Dexbromph niramin-mal at ist.

Patentan prüche für den V rtragstaat : GR

1. Verfahren zur Herstellung einer Vorrichtung für die gesteuerte Freigabe einer odar mahrarer aktiver Substanzen in ein flüssiges Medium in konstanter Menge, umfassend das homogene Dispergieran dieser Substanzen, mit oder ohne einem oder mehraren inerten Arzneistoffträgarn, und das Einschließen darselben in der Form ainer gänglgen zylindrischan Tablette oder eines Bolus mit Hilfe einer all-umschließenden undurchlässigen Wand oder eines Überzuges und Entfernen eines oder mehrerer Streifen von der Wand oder dem Überzug von der Seite der Tablette oder des Bolus.

2. Verfahren nach Anspruch 1, worin die Seite einen Zylinder definiert und die Obar- und Unterseiten konvex sind.

3. Verfahren nach Anspruch 2, worin mehr als ein Streifen der Wand oder des Überzuges von der Seite der Vorrichtung entfernt werden, wobei die entfernten Streifen die gleiche oder unterschiedliche Breiten haben.

4. Verfahren nach einem der vorstehenden Ansprüche, worin die Substanz biologisch aktiv ist.

5. Verfahren nach Anspruch 4, worin die Wirksamkeit der Substanz darin besteht Gerüche in dem oder austratend aus dem flüssigen Medium zu varhindern oder zu reduzlaran, oder die Substanz eine keimtötenda oder pharmakologischa Wirksamkeit hat.

6. Verfahren nach Anspruch 1 der Herstellung eines Bolus für die orale Verabreichung in den Netzmagen oder den Pansen einas wiederkäuenden Säugetieres, wobei der Bolus im Pansen oder Netzmagen zurückgehalten wird und eine oder mehrere aktive Substanzen in die Umgebung im Pansen oder Netzmagen entläßt in einer konstanten Menge über einen längeren Zaitraum.

7. Verfahran nach Anspruch 6, worin die aktiva Substanz Morantel oder ain pharmazeutisch annehmbares Salz davon in einer Polymermatrix ist.

8. Verfahren nach Anspruch 1 der Herstellung einer Tablette zur oralen Verabreichung für ain Säugetier, die eine pharmzeutisch wirksame Substanz in die Flüssigkeit des gastrointastinalen Traktes dieses Säugetieres entläßt in einer konstanten Menge über ein nennenswertes Zeitintervall.

9. Verfahren nach Anspruch 8, worin die Substanz gagen Hypertonie ist.

10. Verfahren nach Anspruch 9, worin die Substanz Prazosin, Nifedipin, Trimazosin odar Doxazosin ist.

11. Verfahren nach Anspruch 8, worin die Sub-

stanz ein Beruhigungsmittel ist.

12. Verfahren nach Anspruch 11, worin die Substanz Hydroxyzin od r Sertralin ist.

13. Verfahren nach Anspruch 8, worin die Substanz ain Bronchodilator ist.

14. V rfahren nach Anspruch 13, worin die Substanz Pirbuterol ist.

15. Verfahran nach Anspruch 8, worin die Substanz ein blutzuckersenkendas Mittal ist.

16. Verfahren nach Anspruch 15, worin die Substanz Glipizid ist.

17. Verfahren nach Anspruch 8, worin die Substanz ein Husten-odar Erkältungsmittel ist.

18. Varfahren nach Anspruch 17, worin dia Substanz Brompheniramin-malaat, Chlorpheniramin-maleat, Phenylephrine-hydrochlorid, Pseudoephedrin-hydrochlorid, Cetirizin- oder Dexbrompheniramin-maleat ist.

Revendications

Revendications pour les Etats Contractants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE, ES

1. Dispositif pour la libération contrôlée d'une ou plusieurs substances actives dans un milieu fluide à une vitesse constante, qui comprend ladite substance dispersée de manière homogène, avec ou sans un ou plusieurs excipients inertes, et présente sous forme d'un comprimé ou bol généralement cylindrique au moyen d'une paroi ou d'un revêtement imperméable à recouvrement total, à l'exception d'une ou plusieurs bandes de paroi ou de revêtement éliminé de la partie latérala dudit dispositif.

2. Dispositif suivant la revendication 1, dans lequel la partie latérale définit un cylindre et la partie supérieure et la partie inférieure sont convexes.

3. Dispositif suivant la revandication 2, dans lequel plus d'une bande de paroi ou de revêtement est éliminée de la partie latérale dudit dispositif, les bandas éliminées ayant des largeurs identiques ou différentes.

4. Dispositif suivant l'une qualconque des revendications précédantes, dans lequel la substance est biologiquement active.

5. Dispositif suivant la revandication 4, dans lequal l'activité da la substance consiste à inhiber ou réduire les odeurs présentes dans le milieu fluide ou émanant de celui-ci, ou bien l'activité de la substance consiste en une activité germicide ou pharmacologique.

6. Dispositif suivant la revendlcation 1, consistant en un bol destiné à l'administration orale dans le réticulum ou le rumen d'un mammifèra ruminant, ledit bol étant retenu dans ledit rumen ou réticulum at libérant une ou plusieurs substances actives dans le milieu présent dans ledit rumen u réticulum à une vit ssa constante pendant un temps prolongé.

7. Bol suivant la revandication 6, dans lequel la substance active est le morantel, ou un d s s sels pharmaceutiquement acceptabl s, dans une matrice polymérique.

8. Dispositif suivant la r vendication 1, consistant en un comprimé, destiné à l'administration orale à un mammifère, qui libère une substance pharmaceutiquement active dans le fluide du tractus gastro-intestinal dudit mammifère à une vitasse constante en un intervalle de temps appréciable.

9. Comprimé suivant la revendication 8, dans laquel la substance est un anti-hypartenseur.

10. Comprimé suivant la revendication 9, dans lequel la substance est la prazosine, la nifédipine, la trimazosine ou la doxazosine.

11. Comprimé suivant la revendication 8, dans lequel la substance est un agent anxiolytique.

12. Comprimé suivant la revendication 11, dans lequel la substance est l'hydroxyzine ou la sertraline.

13. Comprimé suivant la revendication 8, dans lequel la substance est un bronchodilatateur.

14. Comprimé suivant la revendication 13, dans lequel la substance est le pirbutérol.

15. Comprimé suivant la revendication 8, dans lequel la substance est un agent abaissant la teneur sanguine en glucose.

16. Comprimé suivant la revendication 15, dans lequel la substance est le glipizide.

17. Comprimé suivant la ravendication 8, dans lequel la substance est un agent destiné à lutter contre la toux ou le rhume.

18. Comprimé suivant la revandication 17, dans laqual la substance est le maléate de bromphéniramine, la maléate de chlorphéniramine, la chlorhydrate de phényl-éphrine, le chlorhydrate da psaudo-éphédrine, la cétirizine ou le maléate de dexbromphéniramine.

Revendications pour l'Etat Contractant : GR

1. Procédé de production d'un dispositif destiné à la libération contrôlée d'una ou plusieurs substances actives dans un milieu fluide à une vitessa constante, qui consiste à disperser lesdites substances de manière homogène, avac ou sans un ou plusieurs excipients inertes, ledit dispositif contenant lesdites substances essentiallament sous forme d'un comprimé ou bol généralement cylindrique au moyen d'une paroi ou d'un revêtement imperméable à recouvrement total, et à éliminer une ou plusieurs bandes de la paroi ou du revêtement de la partie latérale du comprimé ou bol.

2. Procédé suivant la revandication 1, dans laquel la partie latérale définit un cylindre et la partie supérieure et la partie inférieure sont convexes.

3. Procédé suivant la rev ndication 2, dans laquel

plus d'une bande de paroi ou de revêtement est éliminée d la parti latérale du dispositif, l s band s éliminé s ayant des largeurs identiques ou différentes.

4. Procédé suivant l'une quelconque des r vendications précédentes, dans lequel la substance est biologiquement active.

5. Procédé suivant la revendication 4, dans lequ l l'activité de la substance consiste à inhiber ou réduire les odeurs présentes dans le millieu fluide ou émanant de celui-ci, ou bien l'activité consiste en une activité germicide ou pharmacologique.

6. Procédé suivant la revendication 1, destiné à la production d'un bol pour l'administration orale dans le réticulum ou le rumen d'un mammifère ruminant, ledit bol étant retenu dans ledit rumen ou réticulum et libérant une ou plusieurs substances actives dans le milieu présent dans ledit rumen ou réticulum à une vitesse constante pendant un temps prolongé.

7. Procédé suivant la revendication 6, dans lequel la substance active est le morantel, ou un de ses sels pharmaceutiquement acceptables, dans une matrice polymérique.

8. Procédé suivant la revendication 1, pour la production d'un comprimé destiné à l'administration orale à un mammifère, qui libère une substance pharmaceutiquement active dans le fluide du tractus gastro-intestinal dudit mammifère à une vitesse constante en un intervalle de temps appréciable.

9. Procédé suivant la revendication 8, dans lequel la substance est un anti-hypertenseur.

10. Procédé suivant la revendication 9, dans lequel la substance est la prazosine, la nifédipine, la trimazosine ou la doxazosine.

11. Procédé suivant la revendication 8, dans lequel la substance est un agent anxiolytique.

12. Procédé suivant la revendication 11, dans lequel la substance est l'hydroxyzine ou la sertraline.

13. Procédé suivant la revendication 8, dans lequel la substance est un bronchodilatateur.

14. Procédé suivant la revendication 13, dans lequel la substance est le pirbutérol.

15. Procédé suivant la revendication 8, dans lequel la substance est un agent abaissant la teneur sanguine en glucose.

16. Procédé suivant la revendication 15, dans lequel la substance est le glipizide.

17. Procédé suivant la revendication 8, dans lequel la substance est un agent destiné à lutter contre la toux ou le rhume.

18. Procédé suivant la revendication 17, dans lequel la substance est le maléate de bromphéniramine, le maléate de chlorphéniramine, le chlorhydrate de phényl-éphrine, le chlorhydrate de pseudo-éphédrine, la cétirizine ou le maléate de dexbromphéniramine.

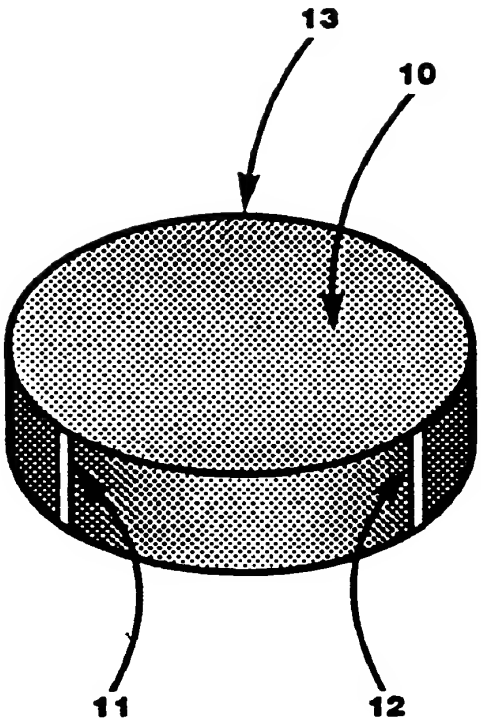


Figure 1

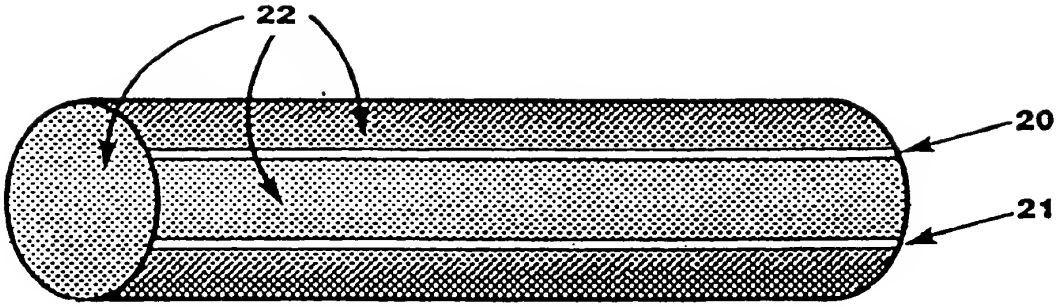


Figure 2

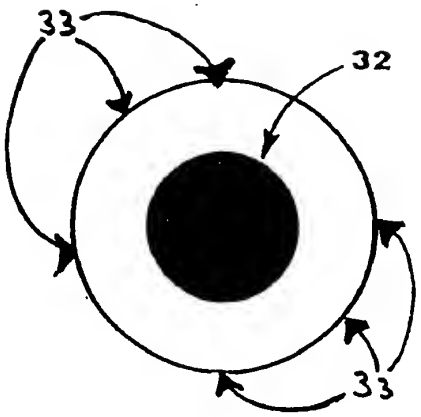
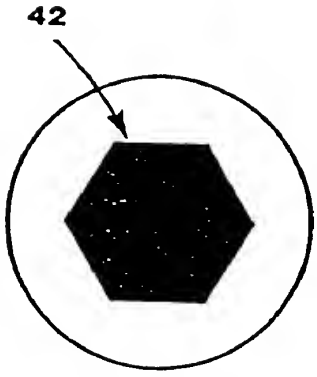


Figure 3



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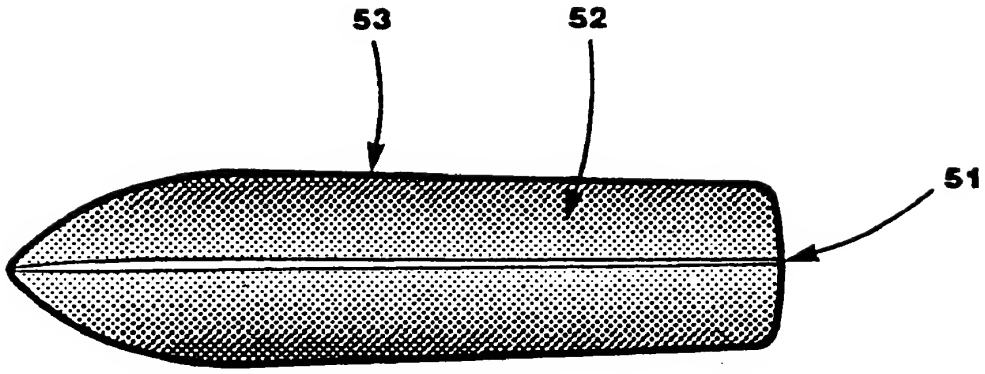

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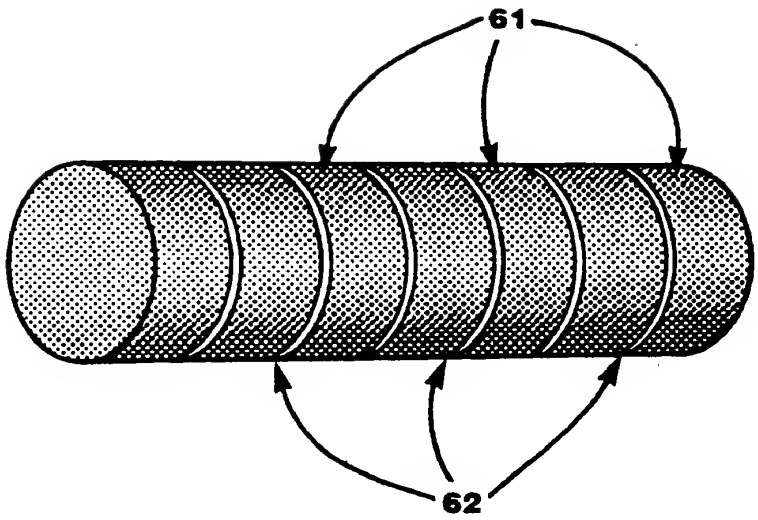

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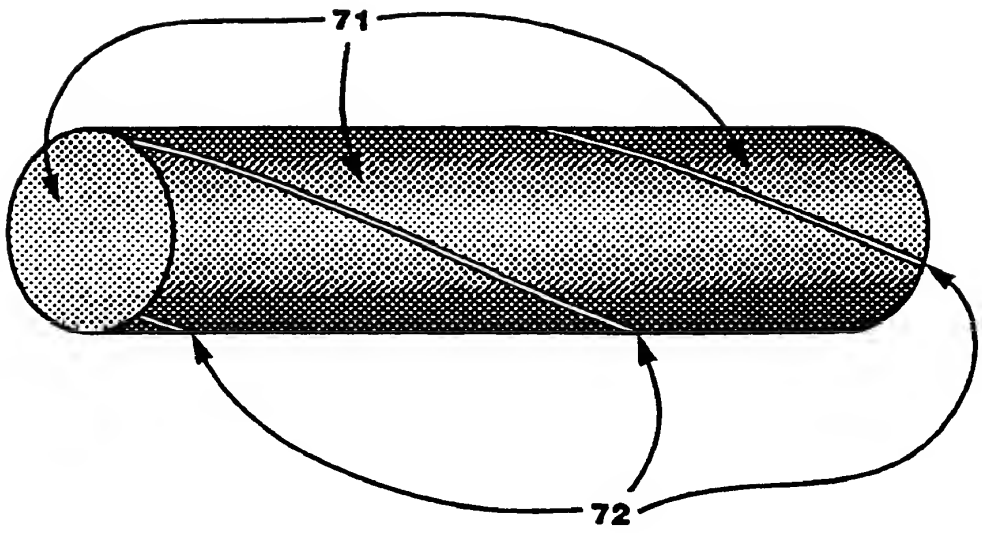

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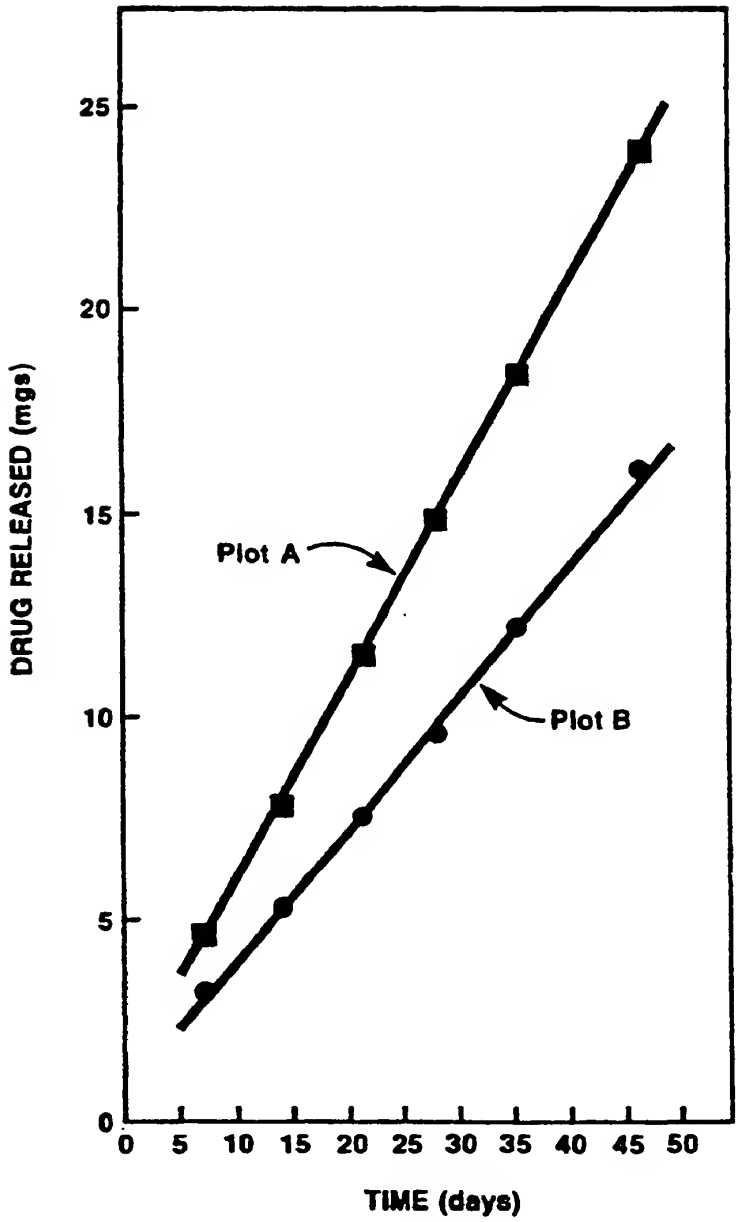
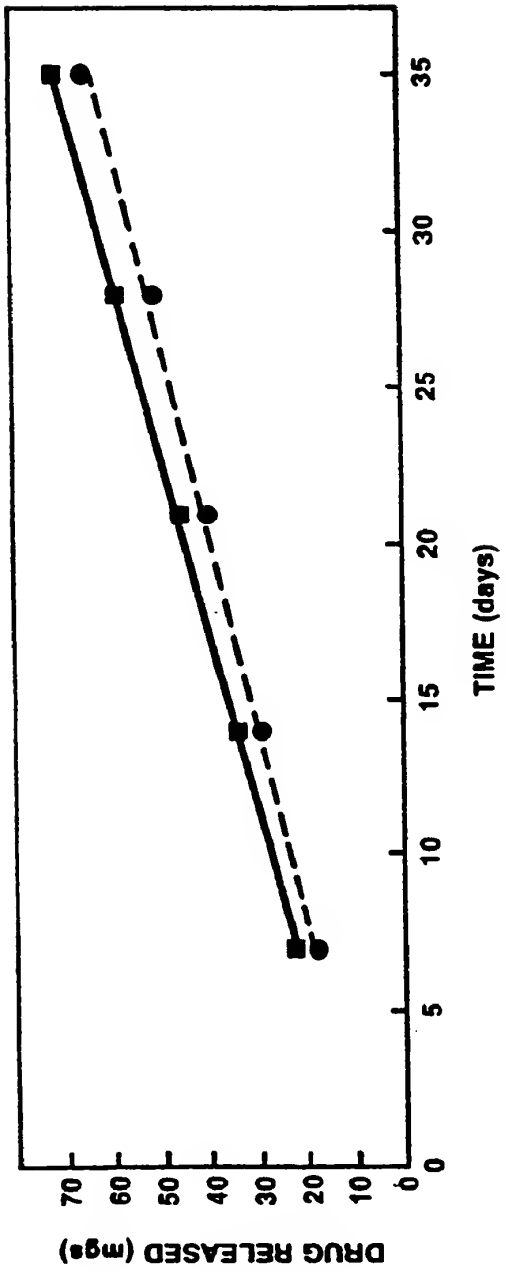

DRUG RELEASED (mgs)
25
20
15
10
5
0
Plot A
Plot B
0 5 10 15 20 25 30 35 40 45 50
TIME (days)

Figure 8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20
25
30
35
TIME (days)

Figure 9

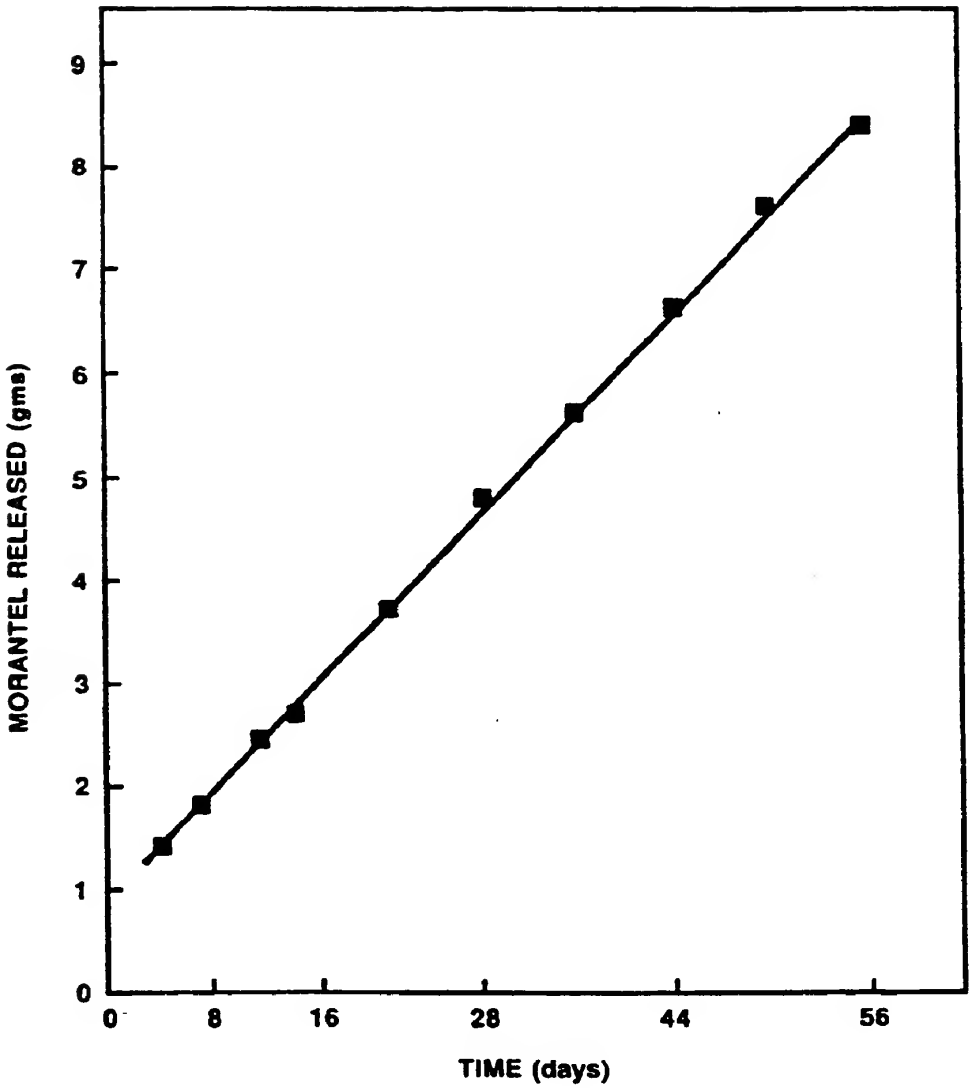

Figure 10

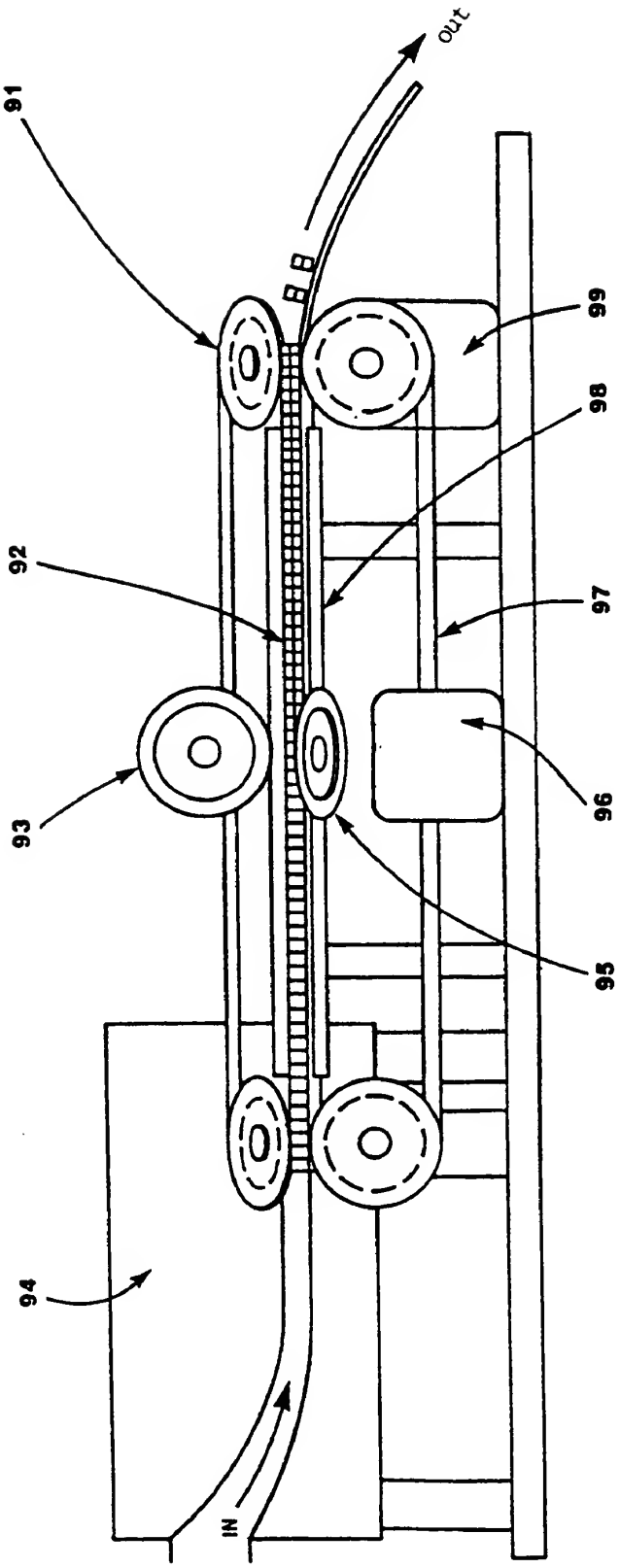

Figure 11

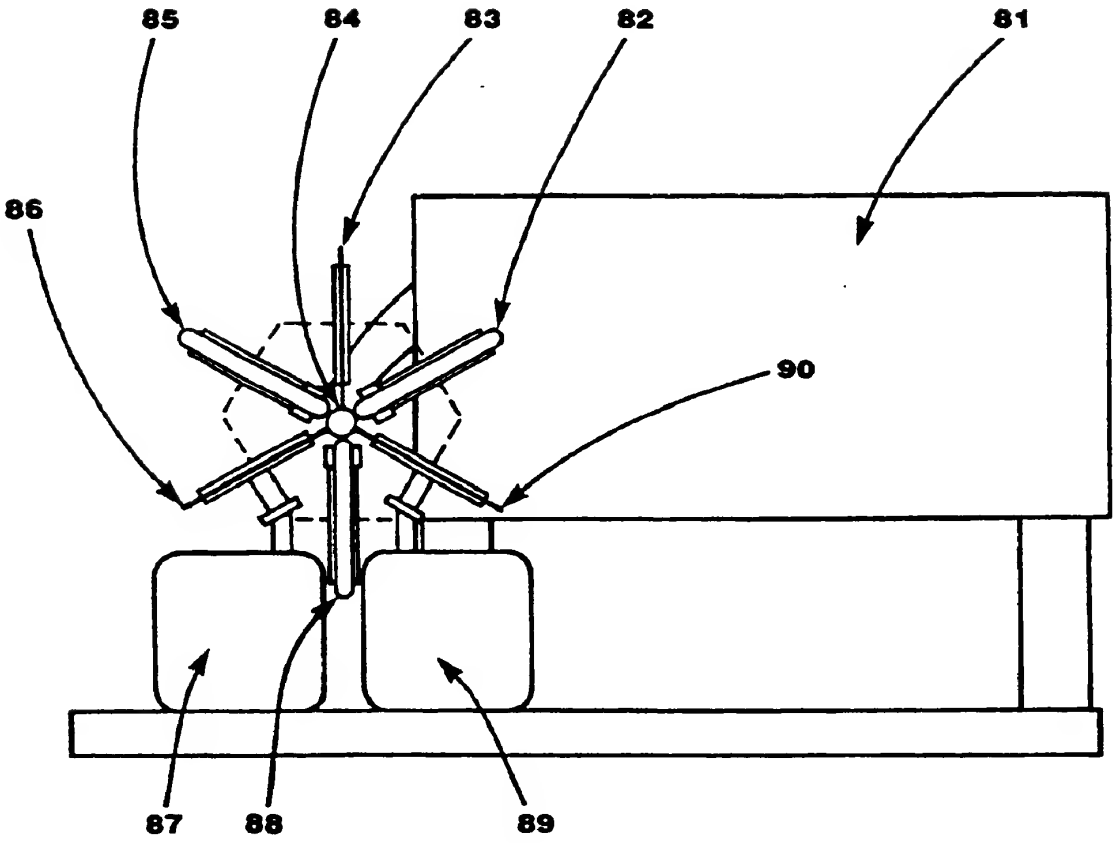

Figure 12